Acute Treatment of Ischemic and Hemorrhagic Stroke: from r-tPA to r-Factor VIIa

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Oncorhynchus lewisi

Goals: Understanding …

- Epidemiology of stroke
- Pathophysiology of stroke
- Importance of public awareness of stroke and aggressive primary care for those at risk
- Emergent management of acute of ischemic and hemorrhagic stroke patients
- Common post-stroke medical complications

What is Stroke?

- 'Stroke'
  - From the Anglo-saxon term '*strIcan'*
  - *"To be struck down"*
- *Apoplectic*, or rapid, onset of brain dysfunction
- Impaired blood flow to the brain, or ischemia
- Insufficient oxygen delivery, or hypoxemia
- Neuronal injury (TIA) or death (stroke)

Epidemiology of Stroke

- 750,000 clinical strokes/yr (q53sec)
- 11 million silent strokes/yr
- Leading cause of disability in US
- Approx 160,000 die (q3.3min)
- 3rd most common cause of death
- 4.5 million stroke survivors alive today
- Costs > $58 billion/yr

Epidemiology of Stroke

- After age 55, risk doubles every 10 yrs
- 75% of all strokes occur in geriatrics
- Important cause of death in children
- Relatively common in young adults
- Under age 45, stroke kills more women than heart attack
- 60% of all SAH occur in women
- 10% of peri/postpartum maternal deaths

TIA Sequelae

- ED diagnosis of TIA
- 1707 pts
- 11% suffered stroke w/in 90days
- 5% suffered a stroke w/in 2days
  - 21% fatal
  - 64% disabling

JAMA 284:2901-6, 2000

Stroke Sequelae

	% Patients	
	1yr	5yrs
Death	15-25	40-60
Recurrent Stroke	10-14	25-40
MI	7	19

Stroke Disability

	%
Hemiparesis	48
Dependence	40
Depression	32
Can’t walk	22
Aphasia	12
Dementia	?

Who's at Risk?

- Risk *markers*
  - Prior TIA or stroke
  - Age
  - Gender
  - Race
- Risk *factors*
  - HTN
  - Diabetes
  - Dyslipidemia
  - Cardiac disease
  - Tobacco use
  - Obesity, sedentary lifestyle
  - Obstructive sleep apnea
  - Hypercoagulability
  - Arrhythmia
  - Prosthetic valves
  - Carotid stenosis

The Problem with Stroke …

- Poor Public Awareness of Stroke Symptoms/Treatment
  - Recent survey of Americans over 50
    - 38% didn't know where strokes occurred in the body
    - 17% couldn't name *one* stroke symptom
    - 19% felt nothing could be done to prevent a stroke
    - 66% didn't know time to treatment was important

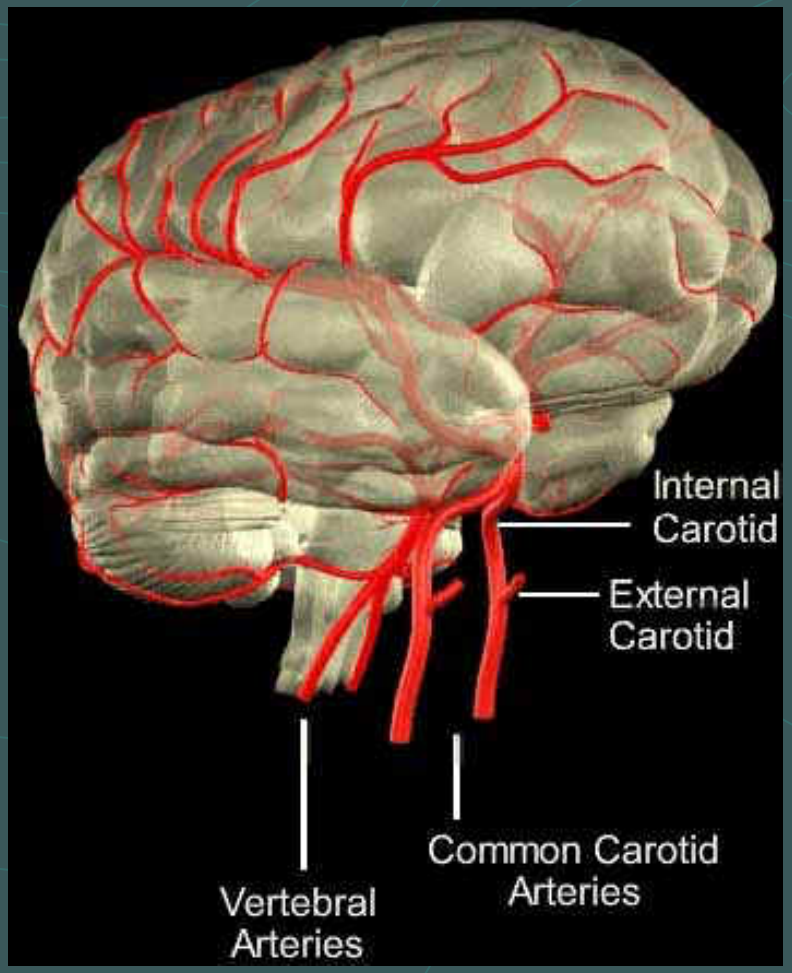
The Problem with Stroke …

- Poor Public Response to Stroke Symptoms
  - Only 40% would call 911 if they though they were having a stroke
  - Most stroke victims don't contact a physician until 24hrs after symptom onset
  - Some hope symptoms will go away
  - Others embarrassed at calling 911
  - Rapid treatment options forever lost

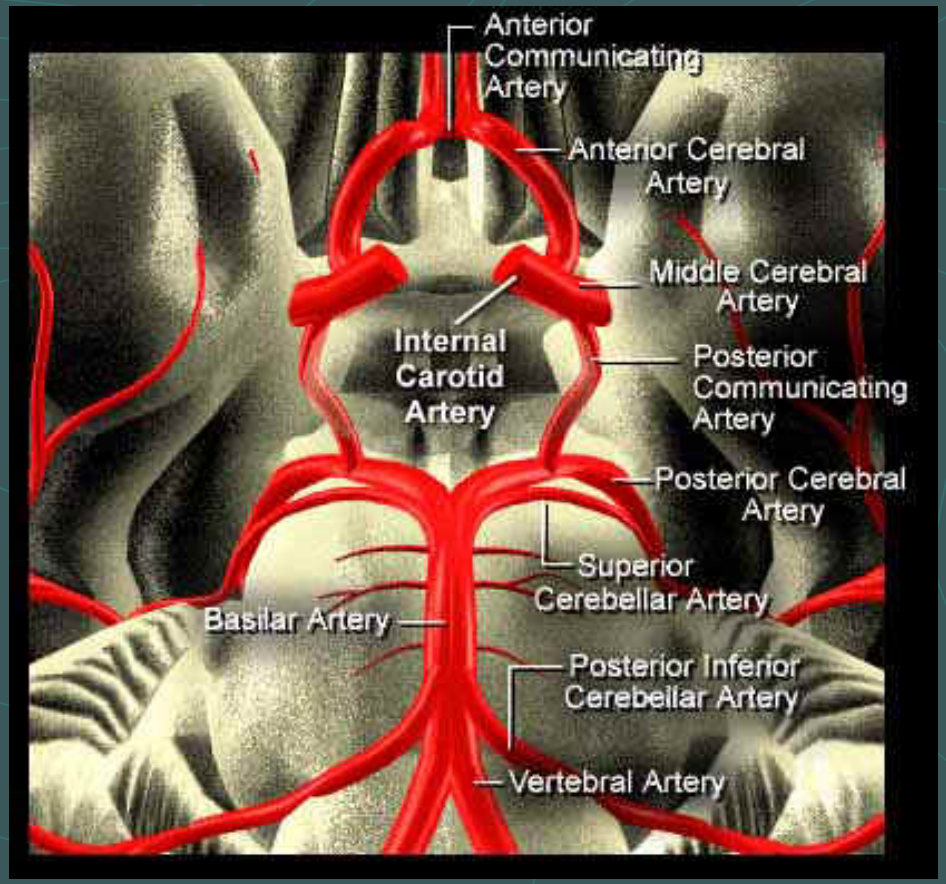
Types of Stroke

- Ischemic 85%
  - Embolic
    - Cardiac
      - Mural thrombi, arrhythmias, valvular heart disease, endocarditis, cardiomyopathies, intracardiac defect
    - Intra-arterial source
      - Ruptured plaque or thrombus from diseased aorta, carotid or vertebrobasilar system

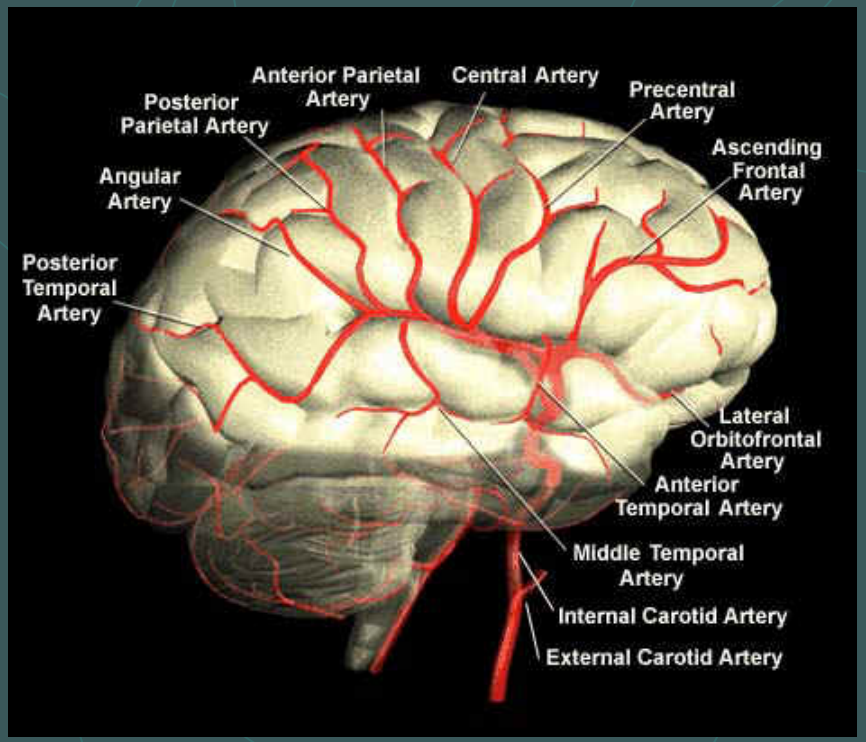
Cerebral Blood Flow

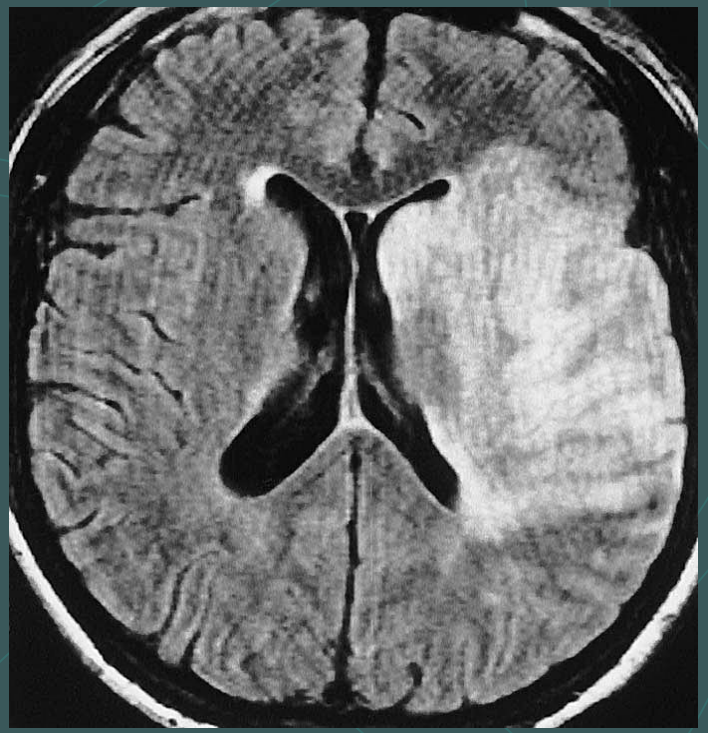


Circle of Willis

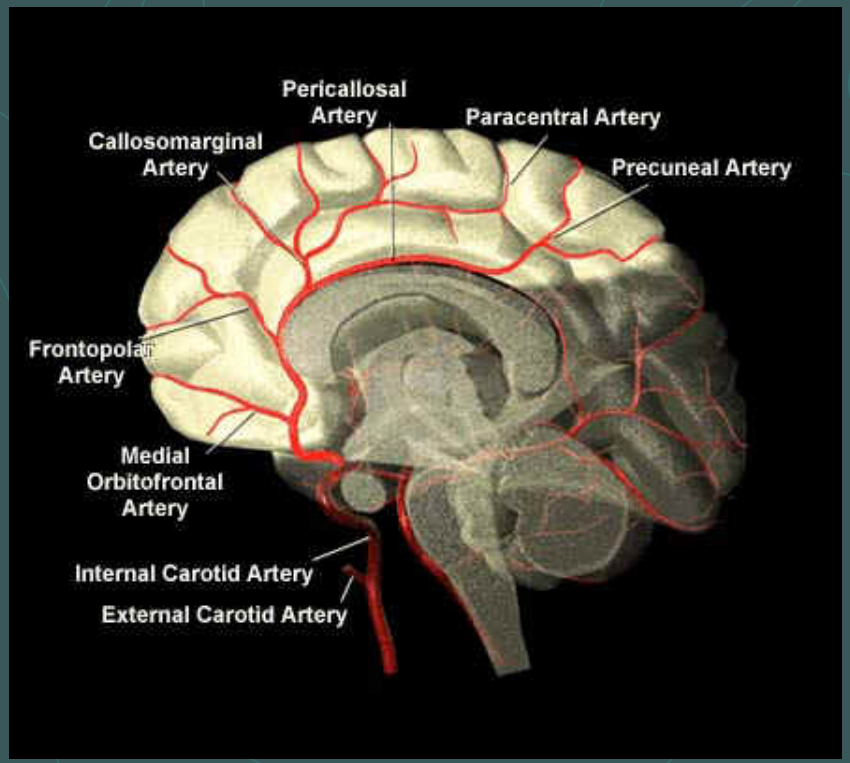


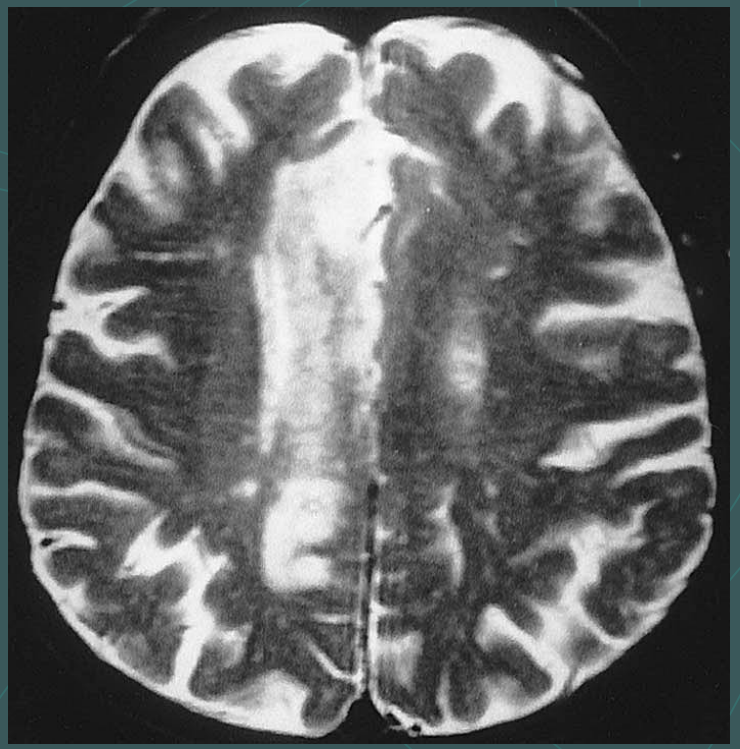
Middle Cerebral Arteries



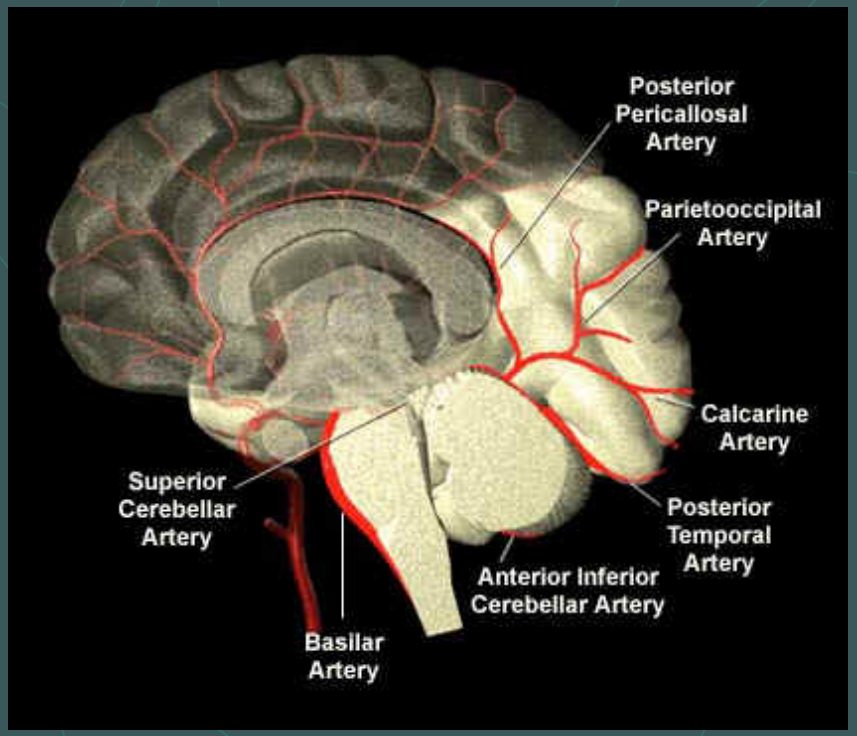


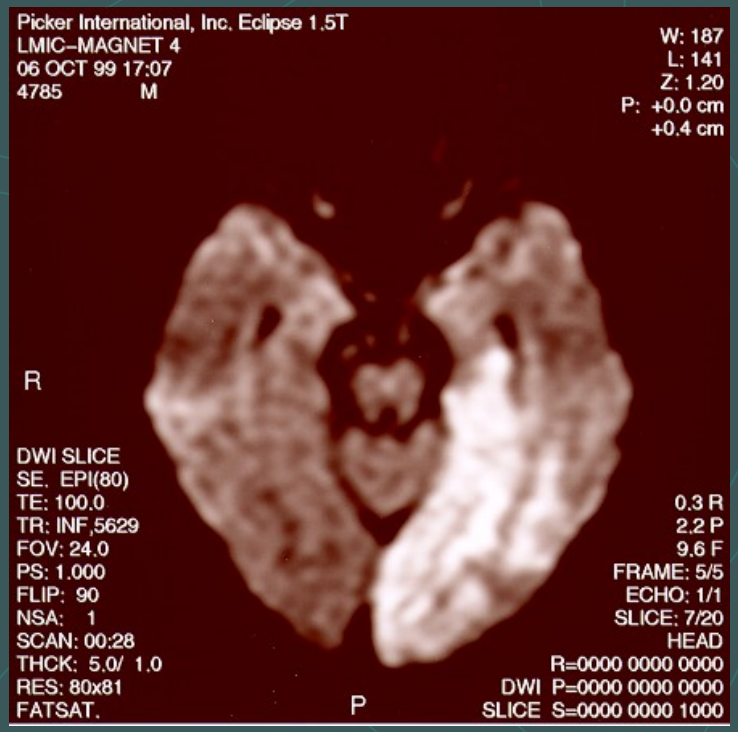
Anterior Cerebral Arteries





Vertebrobasilar System and Posterior Cerebral Arteries

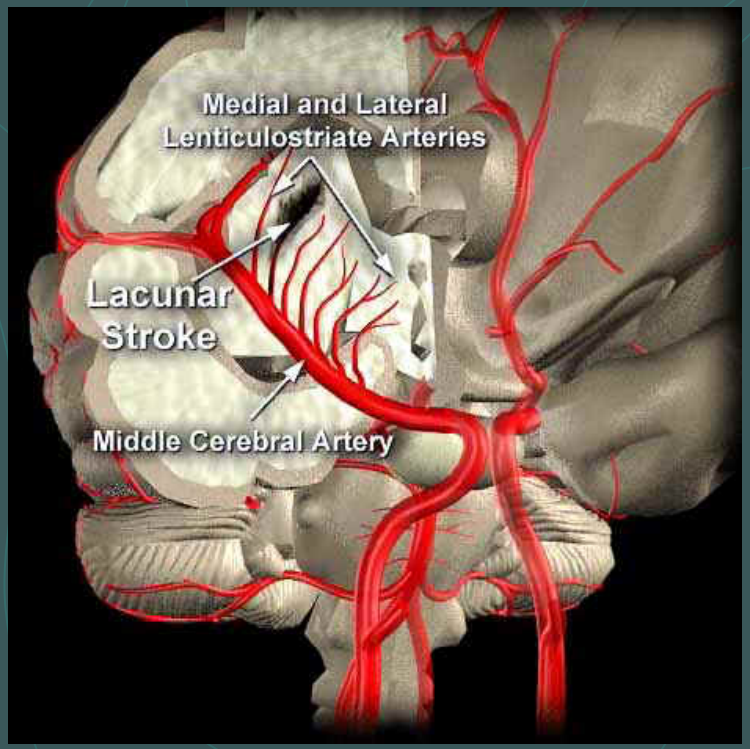


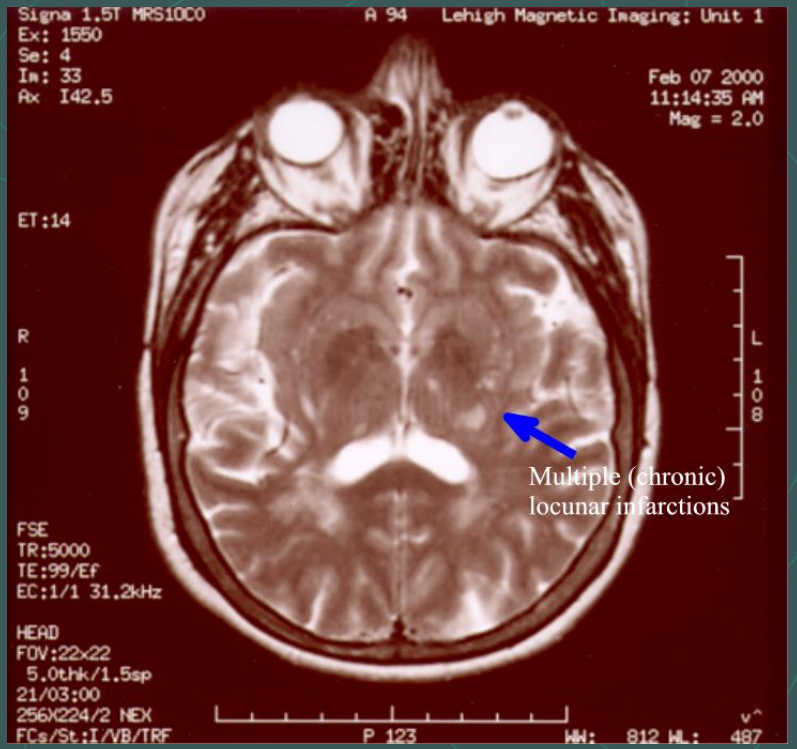


Types of Stroke

- Ischemic 85%
  - Lacunar
    - From the French for “hole”
    - 10-15mm in size
    - Disease of small penetrating arteries
      - HTN – media thickening
      - DM, tobacco, dyslipidemia – intimal disease
    - Rx: Antiplatelets, control the underlying disease state
    - Little else can be done? IVFs …

Lenticulostriate Arteries

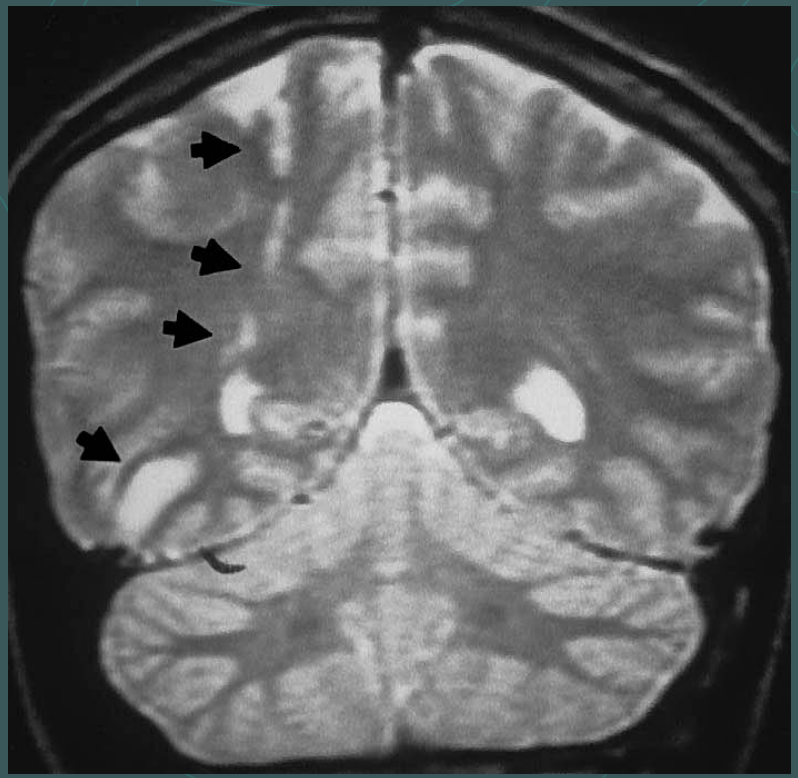


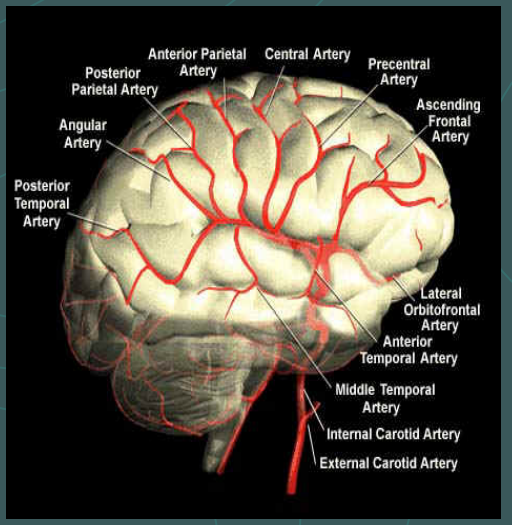


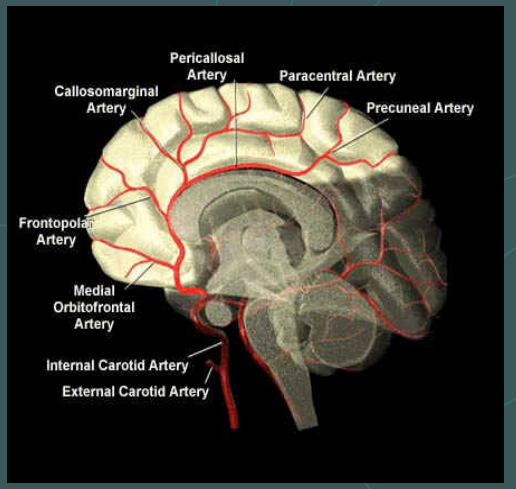
Types of Stroke

- Ischemic 85%
  - Hypoperfusion
    - Atherosclerosis of intra- or extra-cranial arteries
    - Cardiac insufficiency
      - aMI
      - CHF
      - Arrhythmia
      - Arrest
    - Hypotension
    - Hypovolemia
  - ⇒ *"Watershed"* stroke

Watershed Stroke







Types of Stroke

- Hemorrhagic 15%
  - SAH 5%
    - Ruptured aneurysm
    - “Worst HA of life”
    - Dx by CT
    - May require LP
      - Xanthechromia
      - CSF RBC
    - HTN, drugs?
    - PKD, SLE, Ehlers-Danlos

Types of Stroke

- Hemorrhagic 15%
  - ICH 10%
    - 10% US, Europe
    - 20-30% Asia
    - 35-52% die
    - 20% independent @ 6 months

Types of Stroke

- Hemorrhagic 15%
  - ICH 10% (cont)
    - HTN (usually)
    - Microaneurysm in deep penetrating arteries
    - Putamen, caudate nucleus, WM, thalamus, pons, cerebellum

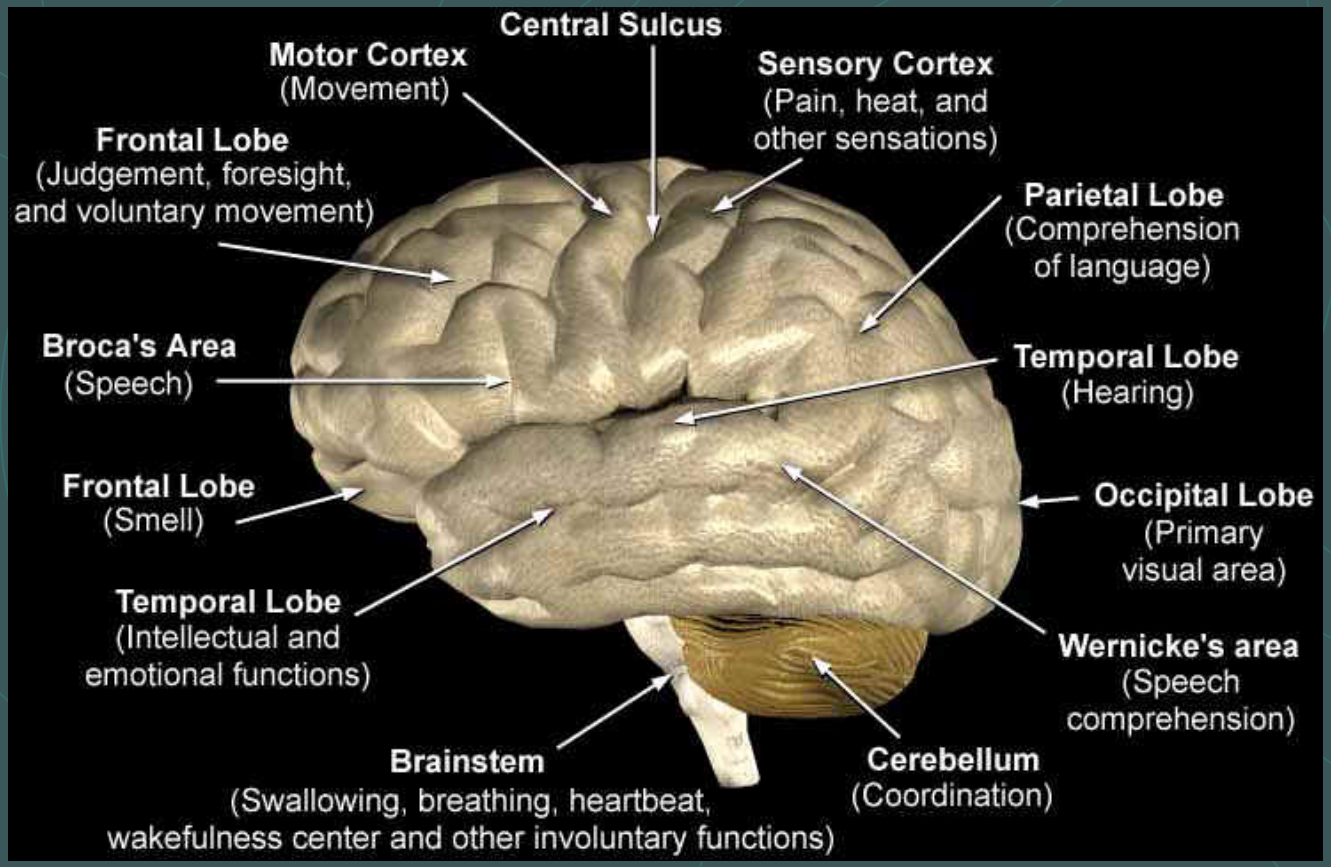
Types of Stroke

- Hemorrhagic 15%
  - ICH 10% (cont)
    - Bleeding disorder
    - Brain tumors
    - Vascular abnormality: amyloidosis, malformation, mycotic aneurysm, etc.
    - Sympathomimetics
    - Trauma

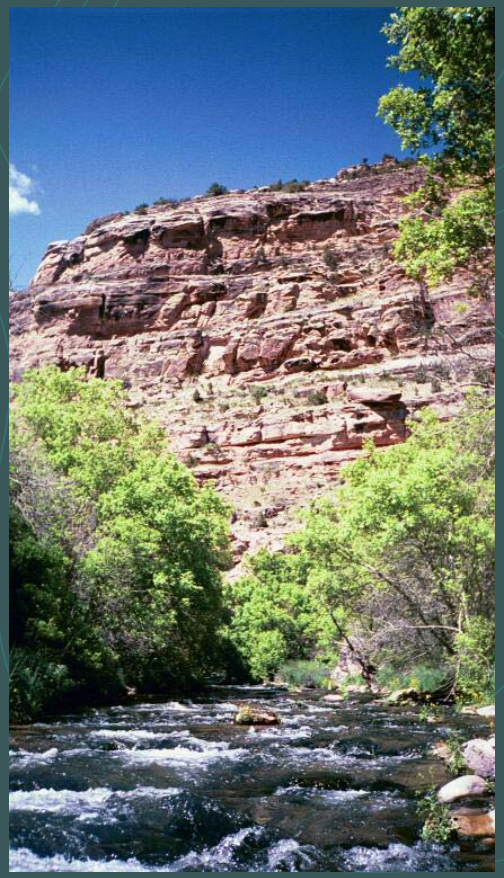
Recognizing Stroke Symptoms

- AMS
- Aphasia
- Dysarthria
- Facial weakness or asymmetry
- Weakness, paralysis, incoordination or sensory loss
- Ataxia, postural instability
- Monocular or binocular visual loss
- Vertigo, diplopia, hearing loss, N/V, (pre)syncope
- HA, photophobia, meningismus

Symptomatology: *Location, location, location*



Oncorhynchus mykiss



Acute Stroke Management

“Time is brain.”

Montana: Who We Are

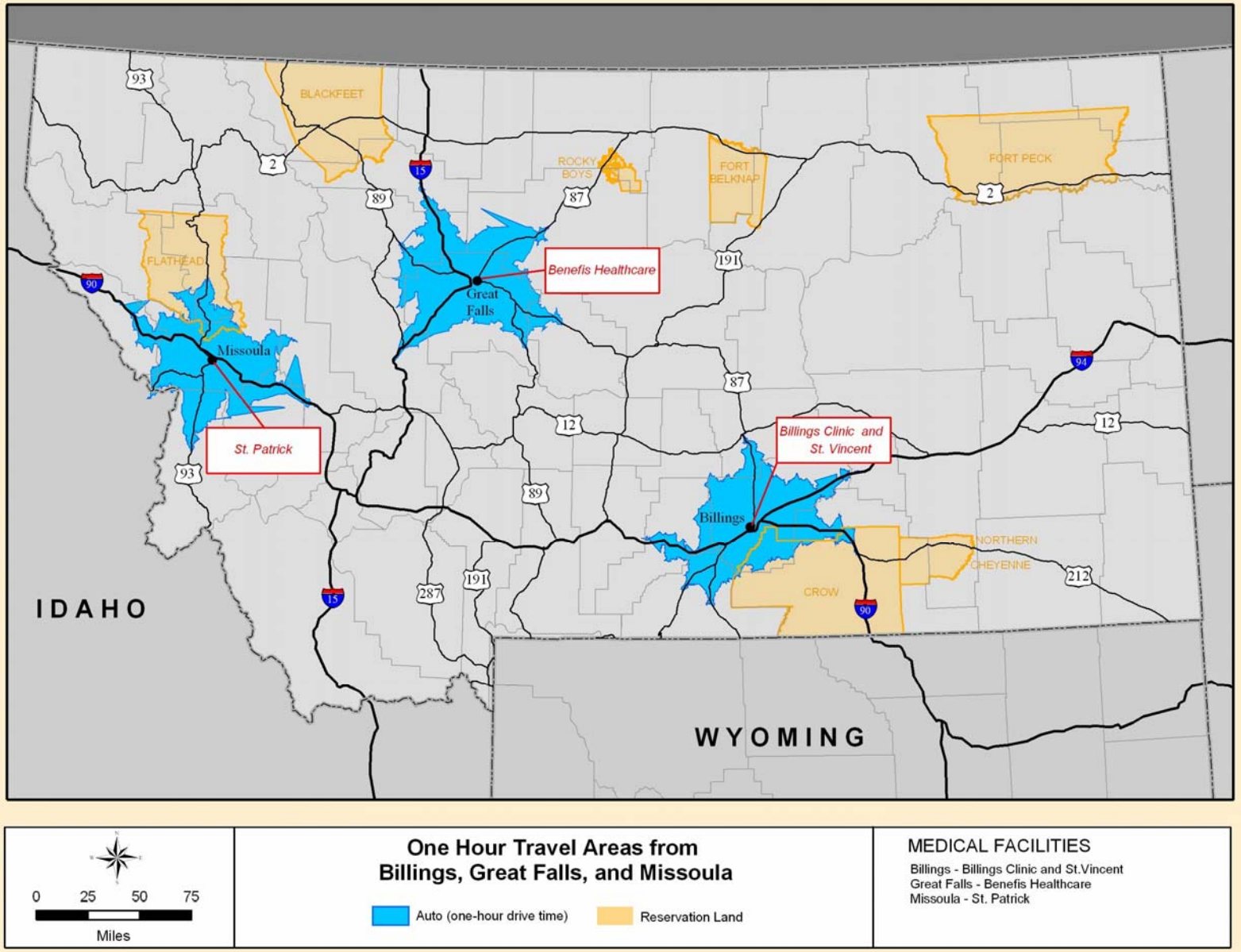
- 4th largest state in nation
  - 147,138 square miles
- 2005 population
  - 935,670
- Population density 48th in nation
  - 6.2 /square mile
- Population age 65 and over
  - 13.7%

Stroke Care in Montana

- Montana Stroke Work Group
- Limited Certified Primary Stroke Centers
  - Billings (2)
  - Great Falls
  - Spokane, WA
- St. Patrick Hospital in Missoula
  - Certification pending

Interventions at St. Patrick Hospital

- Thrombolytics
  - IV & IA
- Vascular
  - CEA
  - Carotid Stenting
- Cardiac
  - PTCA/Stenting
  - PFO Closure
- Neurosurgical
  - Craniotomy/craniectomy
  - Aneurysm Clipping
  - Ventriculostomy


BLACKFEET
ROCKY BOYS
FORT BELKNAP
FORT PECK
FLATHEAD
Benefis Healthcare
Great Falls
Missoula
St. Patrick
Billings Clinic and St. Vincent
Billings
NORTHERN CHEYENNE
CROW
IDAHO
WYOMING
93
2
15
89
87
191
90
94
12
287
212
0 25 50 75
Miles
One Hour Travel Areas from Billings, Great Falls, and Missoula
Auto (one-hour drive time)
Reservation Land
MEDICAL FACILITIES
Billings - Billings Clinic and St.Vincent
Great Falls - Benefis Healthcare
Missoula - St. Patrick

Phases of Emergent Stroke Management

- Phase I: Public recognition of stroke symptoms
- Phase II: EMS triage prior to ED arrival
- Phase III: Rapid evaluation, diagnosis and treatment in the ED

I: Public Recognition

- “Know the signs. Act in time.”
- Call 911 immediately if you experience:
  - Sudden one-sided face, arm or leg numbness or weakness
  - Sudden confusion, trouble speaking or understanding
  - Sudden vision changes
  - Sudden trouble walking, dizziness, loss of balance or coordination
  - Sudden severe headache with no known cause

II: EMS Triage

- ABCs
- VS
- General assessment
- Time last seen well?
- Seizure at onset?
- Cincinnati Scale
  - Facial droop
  - Arm drift
  - Slurred speech

III: ER Stroke Management

- Clinical pathway
- Initial acute stroke order sets
  - Timeline of care
  - Nurse Initiated Orders
  - Physician Initiated Orders
  - TPA Inclusion/Exclusion Criteria
- TPA administration orders
- Admission order sets

Timeline of Care

Last seen normal: _____
Arrival to ED: _____
Seen by ED MD: _____
To CT: _____
Returned from CT: _____
CT report called to ED: _____

Stroke Team: _____
Response times:
CT: _____
Pharmacy: _____
Lab: _____
Neurologist Paged: _____ **Call returned:** _____

Physician Orders

Nurse Initiated

1. ☑ Saline Lock
2. ☑ Labs: CBC, CMP, Protime(INR), PTT, CPK, Troponin (repeat Troponin in 6 hours)
3. ☑ 0.9% Normal Saline IV at KVO **(not D_5W)**
4. ☑ NIH Stroke Scale Score _____
5. ☑ O_2 2L nasal cannula. Increase to keep Sat >90% prn
6. ☑ Fingerstick Glucose

Physician Initiated

1. ☐ Stroke Team Notification for acute stroke (order 12 Lead EKG stat, stroke panel labs stat, notify CT, Stroke Coordinator and Pharmacy)
2. ☐ Stat non-contrast head CT
3. ☐ Stat CTA head/neck
4. ☐ Stat PCXR

Pre t-PA: Systolic BP > 185 OR Diastolic BP >110 for 2 MINUTES (goal is reduction of 10-15%)

a) Labetalol (Trandate®) 10 mg IV over 2 minutes, may repeat every 10 minutes x 3
b) If goal blood pressure of systolic BP < 180 and diastolic BP < 100 not achieved, apply nitroglycerin paste 1 inch

During and after treatment with t-PA, or non candidate for t-PA:

1. Monitor blood pressure – **Keep systolic BP < 180 and diastolic BP < 100 (goal is reduction of 10-15%)**
2. Diastolic BP > 140:
   - Nitroprusside (Nipride®) 0.5 mcg/Kg/min IV infusion as initial dose, increase by 0.5 mcg/Kg/min every 15 minutes, to achieve goal SBP of < 180
3. Systolic BP > 230 OR diastolic BP 121-140
   a) Labetalol 10 mg IV over 2 minutes
   May repeat labetalol every 10 minutes to a maximum dose of 300 mg

   b) If goal blood pressure not achieved, Nicardipine (Cardene®) 5mg/hour IV infusion as initial dose and titrate to desired effect by increasing 2.5mg/hr every 5 minutes to a maximum of 15 mg/hour

_____ MD Date: _____ Time: _____

Patient Label

3. DETERMINE CANDIDACY FOR INTRAVENOUS THROMBOLYTICS:

Inclusion Criteria:	**YES**	**NO**
•Age 18 years or older	☐	☐
•**Clinical Dx** of ischemic stroke causing a measurable NIHSS deficit	☐	☐
•Time of symptom onset well established to be <180 minutes before treatment would begin	☐	☐
•Meets all Inclusion Criteria	☐	☐
Exclusion Criteria:	**Yes**	**No**
Historical:		
•Stroke, serious head trauma or MI in < 3 months	☐	☐
•Major surgery or serious trauma last 14 days	☐	☐
•History of Intracerebral hemorrhage, AVM, neoplasm or aneurysm	☐	☐
•GI or urinary tract hemorrhage in last 21 days	☐	☐
•Noncompressible arterial puncture or LP last 7 days	☐	☐
Clinical:		
•Rapidly improving or minor signs/symptoms	☐	☐
•SBP>185 or DBP > 110 repeatedly, or aggressive IV treatment to reduce BP	☐	☐
•Seizure at the onset of stroke symptoms	☐	☐
•Symtoms suggestive of subarachnoid hemorrhage *(even if non-contrast head CT negative)*	☐	☐
• MI-induced pericarditis	☐	☐
Diagnositic:		
• Active bleeding on non-contrast head CT	☐	☐
• Intracerebral hemorrhage on non-contrast head CT	☐	☐
• Protime >15 seconds, INR >1.7, Or on oral anti-coagulants	☐	☐
•Heparin Rx w/in 48 hs w/PTT elevated >upper limit	☐	☐
•Platelets < 100,000/mm3	☐	☐
•Blood glucose < 50 or > 400 mg/dl		
•Pregnancy w/in 30 days	☐	☐

4. ADMINISTRATION OF t-PA ? ? ☐ **t-PA not indicated (use stroke order set not-PA given)**

St. Patrick Hospital and Health Sciences Center

Thrombolytic Therapy with Alteplase (t-PA) for Ischemic Stroke

Allergies: _____

Admit to: _____ Admit as: Inpatient ☐ Observation ☐

Diagnosis: _____ Age: _____ Weight: _____ Kg

ADMINISTRATION OF ALTEPLASE (t-PA) INDICATED: (See Initial Orders for Adult Acute Stroke)

1. Alert pharmacy immediately when considering alteplase for a stroke patient. Call with name and weight. _____ Kg

2. Start two saline locks if not already done, including one #16 gauge lock in antecubital fossa.

3. Begin alteplase at 0.9 mg/Kg with a maximum dose of 90 mg made as a 1 mg/ml solution. Give 10 percent of the dose as a bolus over one minute, then the remaining 90 percent over 59 minutes. (see attached table)

   Bolus dose = _____ mg which is _____ milliliters bolus over one minute.

   Remaining dose = _____ mg which is _____ milliliters over 59 minutes.

4. Alteplase start date and time _____

5. Vital signs with neurological checks are to be performed and documented before the initiation of alteplase therapy and every 15 minutes thereafter.

6. IF PRETREATMENT Systolic BP > 185 OR Diastolic BP > 110 for 2 MINUTES call MD <u>and</u> proceed with the below:

   a) Labetalol (Trandate®) 10 mg IV over 2 minutes, may repeat every 10 minutes x 3
   b) If goal blood pressure of systolic BP < 180 and diastolic BP < 100 not achieved, apply nitroglycerin paste 1 inch

7. No anticoagulants or antiplatelets for the next 24 hours.

8. If the patient experiences a sudden decline in neurological status, or new onset of hemorrhage (GI,GU, etc.) <u>STOP</u> the infusion of alteplase and notify the Attending Physician immediately.

Physician Signature _____ Date _____ Time _____

Weight (kg)	Total Dose	Bolus Dose	Remaining Dose	Weight (kg)	Total Dose	Bolus Dose	Remaining Dose
40.0	36.0	3.6	32.4	71.0	63.9	6.4	57.5
41.0	36.9	3.7	33.2	72.0	64.8	6.5	58.3
42.0	37.8	3.8	34.0	73.0	65.7	6.6	59.1
43.0	38.7	3.9	34.8	74.0	66.6	6.7	59.9
44.0	39.6	4.0	35.6	75.0	67.5	6.8	60.7
45.0	40.5	4.1	36.4	76.0	68.4	6.8	61.6
46.0	41.4	4.1	37.3	77.0	69.3	6.9	62.4
47.0	42.3	4.2	38.1	78.0	70.2	7.0	63.2
48.0	43.2	4.3	38.9	79.0	71.1	7.1	64.0
49.0	44.1	4.4	39.7	80.0	72.0	7.2	64.8
50.0	45.0	4.5	40.5	81.0	72.9	7.3	65.6
51.0	45.9	4.6	41.3	82.0	73.8	7.4	66.4
52.0	46.8	4.7	42.1	83.0	74.7	7.5	67.2
53.0	47.7	4.8	42.9	84.0	75.6	7.6	68.0
54.0	48.6	4.9	43.7	85.0	76.5	7.7	68.8
55.0	49.5	5.0	44.5	86.0	77.4	7.7	69.7
56.0	50.4	5.0	45.4	87.0	78.3	7.8	70.5
57.0	51.3	5.1	46.2	88.0	79.2	7.9	71.3
58.0	52.2	5.2	47.0	89.0	80.1	8.0	72.1
59.0	53.1	5.3	47.8	90.0	81.0	8.1	72.9
60.0	54.0	5.4	48.6	91.0	81.9	8.2	73.7
61.0	54.9	5.5	49.4	92.0	82.8	8.3	74.5
62.0	55.8	5.6	50.2	93.0	83.7	8.4	75.3
63.0	56.7	5.7	51.0	94.0	84.6	8.5	76.1
64.0	57.6	5.8	51.8	95.0	85.5	8.6	76.9
65.0	58.5	5.9	52.6	96.0	86.4	8.6	77.8
66.0	59.4	5.9	53.5	97.0	87.3	8.7	78.6
67.0	60.3	6.0	54.3	98.0	88.2	8.8	79.4
68.0	61.2	6.1	55.1	99.0	89.1	8.9	80.2
69.0	62.1	6.2	55.9	100.0	90.0	9.0	81.0
70.0	63.0	6.3	56.7	>100	90.0	9.0	81.0

Allergies:_____ Weight:_____Kg

Admit to:_____ Admit as: ☐ Inpatient ☐ Observation Diagnosis: ☐ Hemorrhagic Stroke ☐ Ischemic Stroke

Date and time when IV t-PA was initiated (if applicable):_____

Draw a line through orders that are not to be implemented.

Code Status: _____: Condition: ☐ Good ☐ Fair ☐ Serious ☐ Critical

Notify_____ of admission

☑ Neuro Checks : every 1 hour x 4 after admission, then every 4 hours. IF in ICU: per ICU standards

Call MD immediately for any change in neurological status

☑ Vital Signs: (BP, HR, T, RR, Sa O2) every 1 hour x 4 after admission; then every 4 hours.
IF in ICU: per ICU standards

☑ Oxygen protocol

☑ I.V. fluids: 0.9% Normal Saline with 20 mEq KCl @ _____mL/hour **OR**_____

☑ Incentive spirometry: every 2 hours while awake (if patient is able to perform)

Diet and I/O:

☐ NPO due to aspiration risk, consult speech therapy for bedside swallow evaluation

☐ Low cholesterol/low sodium diet

☐ Other: _____

☐ Daily Weights

☐ Foley catheter (placed **prior to** thrombolytic administration)

☐ _____

Precautions:

☐ Seizures ☐ Falls

Activity:

☐ Bedrest with HOB @ 30 degrees:

☐ Other: _____

Consults:

☑ Speech therapy for evaluation and treatment

☑ Physical therapy evaluation and treatment

☑ Occupational therapy evaluation and treatment

☐ Nutrition consult

☐ Social Services consult

☐ Rehab MD Consult

Admission Labs **(if not done in ER)**:

☑ CBC, CMP, Protime/INR, PTT
☐ Hypercoagulation Panel
☐ CRP
☐ Other:_____
☐ Mg ++
☐ Phosphorus
☐ ANA
☐ ESR

A.M. Labs (for next day only):

☑ BMP
☑ Lipid panel, fasting
☐ Protime/INR
☐ PTT
☐ Other: _____
☐ CBC w/diff
☐ Homocysteine, fasting
☐ Lipoprotein (a), fasting
☐ Hepatic function panel

Medications:

Guidelines for lowering BP
Ischemic: SBP ? 230 or Diastolic ? 100
Hemorrhagic: SBP ? 180 or Diastolic ? 100

? NO HEPARIN, NO ASPIRIN UNTIL 24 HOURS AFTER INFUSION OF t-PA

BP control:

- ☐ **1st line agent: Labetalol (Trandate®) 10mg IV** over 2 minutes for Systolic BP ? _____ OR diastolic ? ____ May repeat Labetalol (Trandate®) every 10 minutes to a maximum dose of 300 mg
- ☐ **2nd line agent: Nicardipine (Cardene®) 5mg/hour IV** May increase by 2.5mg/hour every 5 minutes to a maximum of 15mg/hour for Systolic BP ? _____ OR diastolic ? _____
- ☐ Vasotec (Enalaprilat®) 0.625-1.25 IV every 1 hour prn for Systolic BP ? _____ OR diastolic ? _____
- ☐ _____

Anticoagulants:

- ☐ Heparin 5000 Units subcutaneously every 12 hours Start date: _____
- ☐ Heparin 5000 Units subcutaneously every 8 hours Start date: _____
- ☐ _____

Antiplatelets:

- ☐ Aspirin 325 mg po/PR daily Start date: _____
- ☐ Clopidogrel (Plavix®) 75 mg po daily
- ☐ _____
- ☐ _____

Others:

- ☐ Famotidine (Pepcid®) 20 mg po/IV every 12 hours
- ☐ Docusate (Colace®) 100 mg po every 12 hours
- ☐ Acetaminophen (Tylenol®) 650 mg po every 4 hours prn pain or temp >38.5
- ☐ Insulin (sliding scale) Refer to hospital order set NS0575-"DOAPS"

DVT Prophylaxis:

- ☐ TED hose, SCD's (while in bed)
- ☐ Dalteparin (Fragmin®) 5000 units subcutaneously daily
- ☐ _____

Diagnostic tests:	Now	AM
MRI – *indication: Stroke*	☐	☐
MRA of head and neck vessels – *indication: Stroke*	☐	☐
12 lead ECG	☐	☐
CT head – *indication: Stroke*	☐	☐
CTA head and neck – *indication: Stroke*	☐	☐
CXR PA/lat – *indication: possible pulmonary disease*	☐	☐
ECHO – *indication: Source of emboli*	☐	☐
Carotid Ultrasound – *indication: possible stenosis*	☐	☐

Signature _____ Date _____ Time _____

Documentation: “Time is Brain”

- Exact onset of symptoms
- Time of arrival to ED
- Time to ED physician
- NIHSS
- Time to CT
- CT read time/report to ED time
- TPA considered in ischemic strokes

Emergent Treatment of Ischemic Stroke

? t-PA ?

IV t-PA Inclusion Criteria

- Age 18 or older
- Clinical diagnosis of ischemic stroke, measurable NIHSS deficit
  - “Mild” strokes do poorly w/o t-PA
- Time of onset 180min before treatment would begin

IV t-PA Exclusion Criteria

- History
  - Stroke, serious head trauma or intracranial operation last 3mo
  - Major surgery or serious trauma last 14d
  - H/O ICH, AVM, or aneurysm
  - GI or urinary tract hemorrhage last 21d
  - Noncompressible arterial puncture or LP last 7d
- Clinical
  - Rapidly improving or minor signs/symptoms
  - SBP > 185mmHg or DBP > 110mmHg repeatedly, or aggressive (IV) treatment to reduced BP

IV t-PA Exclusion Criteria

- Clinical (cont)
  - Seizure at onset of symptoms
  - Symptoms suggestive of SAH (*even if NCHCT negative*)
  - Recent MI-induced pericarditis
- Diagnostics
  - ICH on NCHCT
  - PT > 15 sec, INR > 1.7
  - On heparin w/in 48hrs, PTT elevated (> normal upper limit)
  - Platelets < 100,000/mm^3
  - Blood glucose < 50 or > 400 mg/dl
  - + β-HCG

IV t-PA in Acute Stroke Treatment

- t-PA 0.9 mg/kg IV total, max dose 90mg
  - 10% bolus over 1-2min, document starting time
  - Remaining 90% over 1 hr by infusion pump
- Direct ICU admit
- No Foley catheter until 30 min after t-PA completed
- No NGT until 24 hrs after t-PA completed
- No anticoagulant/antiplatelet agents for 24 hrs after start of t-PA infusion

t-PA & Blood Pressure Management

- IVF: NS @ 100cc/hr
- Keep SBP < 185mmHg, DBP < 105mmHg
  - BP q15min x 2 hrs, then q30min x 6 hrs, then q1hr x16hrs
  - SBP 180-230mmHg or DBP 105-120mmHg:
    - Labetalol 10mg iv over 1-2 min
    - Monitor q10min
    - Repeat 10-20mg q10-20min PRN to 150mg
  - IV nitroprusside for SBP > 230mmHg or DBP > 140mmHg or inadequate response to labetalol

t-PA & Blood Pressure Management

- Caveats
  - <u>AVOID HYPOTENSION</u>
    - $\Rightarrow$ Extends ischemic penumbra
    - $\Rightarrow$ Watershed
  - re-NCHCT R/O ICH
    - If BP rises acutely … *Cushing's response?*
    - *Rapid mental status change*
    - *Blown pupil or other exam changes*

IA t-PA

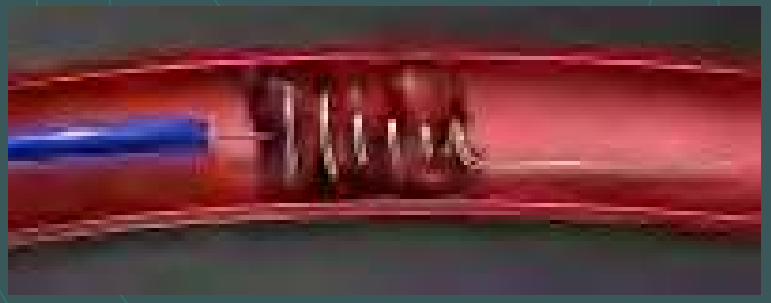
- Interventional Neuroradiology
- Intra-arterial delivery of t-PA
- Extends window to 6hr
- Requires defined lesion
- Less drug can be used
- Can be used in combination with IV t-PA

Intra-arterial t-PA

Mechanical Thrombolysis

- For patients outside the window or with other contraindications to t-PA
- Endovascular technique
- MERCI
  - Mechanical Embolus Removal in Cerebral Ischemia
- FDA approved
- Clot must be visualized and accessible

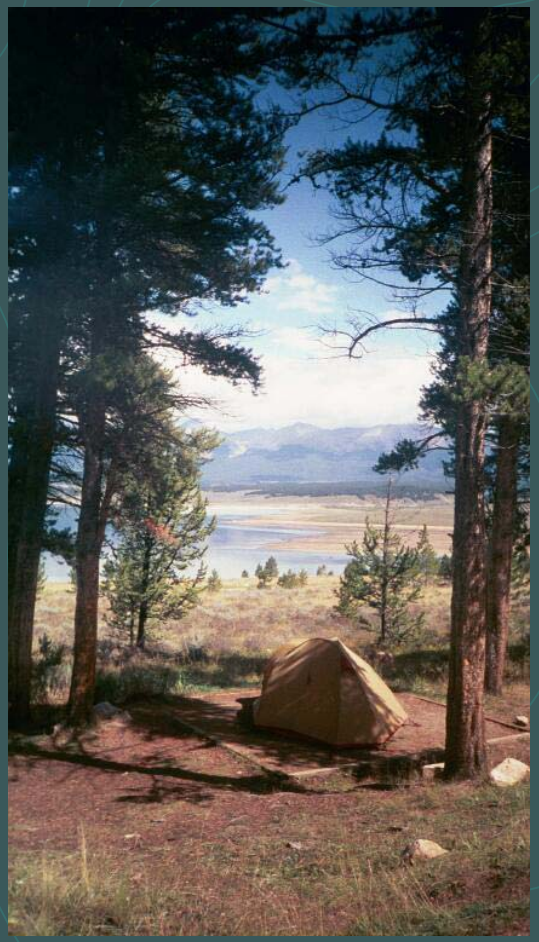
MERCI



What if exclusion criteria are met?

- Antithrombotic or antiplatelet Rx
  - Heparin?
  - LWMH, Heparinoids?
  - ASA, Aggrenox, or Plavix?
  - Supportive care only?
- Rationale: reduce risk for …
  - Stroke progression
  - Recurrent cerebral thromboembolism
  - Venous thromboembolic complications (DVT/PE)

Oncorhynchus mykiss



Emergent Treatment of Hemorrhagic Stroke

? ???? ?

Aneurysmal Subarachnoid Hemorrhage

- Ventilatory support
- IVF: 2-3 liters 0.9% NaCl per 24hr
- Target MAP </= 130mm Hg
  - PRN Labetalol, enalarpilat
- Pain control: Tylenol 3, ultram
- Nutrition: enteral feeding on day 2
- Dilantin ?
- Nimodipine 60mg 6x/day x 21 days
- Surgically clips, interventional coils

Deterioration with SAH

- Rebleeding
- Delayed cerebral ischemia: vasospasm
- Acute hydrocephalus
- Temporal lobe hematoma enlargement

Rebleeding in SAH

- Aneurysm re-ruptures, often within 24hr
- Symptoms
  - LOC
  - Loss brain stem reflexes
  - Respirartory irregularities
- 50% mortality vs. rapid recovery
- Dx: CT
- Tx: Emergency clipping
  - Supportive care

Symptomatic Vasospasm in SAH

- Delayed cerebral ischemia
- Symptoms
  - Gradually diminished consciousness
  - Hemiparesis, apraxia
  - Mutism, apathy
- Less common with endovascular than clipping
- Dx: transcranial Doppler, SPECT, angiography
- Tx: volume repletion, pressors, angioplasty

Acute Hydrocephalus in SAH

- Ventricular outflow obstruction
- Symptoms
  - Gradually diminished consciousness
  - Tachypnea
  - Pinpoint pupils, downward gaze
- Dx: CT progressive ventricular enlargement
- Tx: Ventriculostomy
  - May need permanent shunt

Intracerebral Hemorrhage

- Types
  - Ganglionic
  - Lobar
  - Brainstem
  - Cerebellar
- Presentation
  - Rapid neurological deficit, emesis, fluctuating alertness
  - Symptoms vary, reflect location
  - *Seizures in 30% of lobar hemorrhages*

Intracerebral Hemorrhage

- CT/CTA
- MRI/MRA/MRV
  - Metastasis
  - AVM, cavernous angioma
  - Amyloid angiopathy
  - Cerebral venous thrombosis
- Coags, fibringen, D-dimer; ? Tox screen, ESR, blood cultures

Intracerebral Hemorrhage

- *No effective treatment*
- Surgical = medical support
- Central Issues
  - Herniation management
  - Increased ICP
  - Uncontrolled hypertension
  - Coagulopathy
  - AVM repair

Supportive Treatment in ICH

- Ventilatory support
- Target MAP </= 130mm HG
  - PRN enalapril, labetolol
  - (Pearl: ACE-I dilate cerebral blood vessels in chronic hypertensives)
- Intracranial pressure monitoring
  - Target CPP > 60 mmHG
- Osmotherapy
  - IVF 0.9% maintenance
  - 3% NaCl or Mannitol if rapid decline

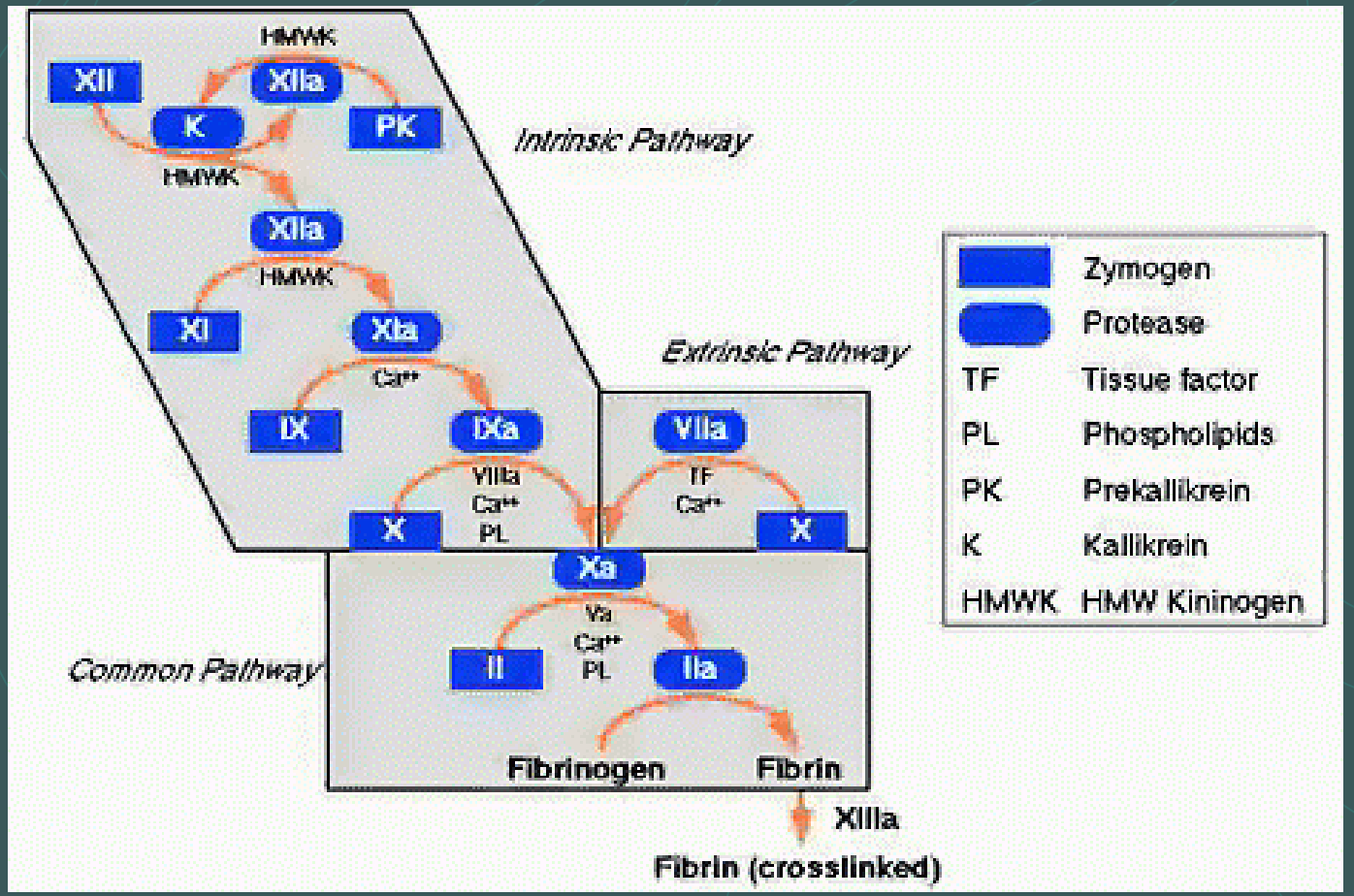
Supportive Treatment in ICH

- Fever control
- Fosphenytoin 20mg/kg in lobar and increased ICP
  - (No phenytoin load unless central line)
- Nutriotional Support
  - Enteral feeding after day 2
- Anticoagulation-related
  - Coumadin: 2 units FFP, vitamin K 2-10mg IV
  - Heparin: Protamine 1mg/100 U heparin
- NO STEROIDS!

Investigational Rx for ICH

- Pathophysiology of hematoma growth after ICH
- Re-bleeding occurs within first few hours
- Less edema than in ischemic strokes
- Associated with poor outcome
- Little hematoma growth after 6 hrs
- Goal: emergent hemostatic therapy
  - Possible equivalent to t-PA in ischemic stroke

Coagulation Cascade



r-Factor VIIa for ICH

- Recombinant version of an initiator of hemostasis
- Developed for Hemophilia A or B and other blood disorders
- Binds activated platelets, tissue factor
- Generates activated Factor X
- Enhances local hemostasis
- Low systemic coagulation activation
- Short $t_{1/2}$

r-Factor VIIa for ICH

- Activates extrinsic pathway
- Warfarin prolongs PT, not PTT
  - Hence effects extrinsic pathway
- R-Factor VII can normalize INR in minutes
- Short lived, dose dependent
- Interest in ICH in anticoagulated patients
- FAST Trial ongoing – phase III

r-Factor VIIa for ICH

- Recombinant Activated Factor VII Trial
  - New Eng J Med 352: 777-785, 2005
  - 3hr window
  - Placebo vs. 40, 80, or 160mcg/kg r-Factor VIIa
  - Outcomes: ICH size @ presentation vs. 24hrs, functional outcomes, death
  - 34% increased volume placebo vs. 13% drug
  - 29% died placebo vs. 18% drug
  - Improved functional outcome
  - Adverse thromboembolic events 2% placebo vs. 7% drug

Stroke Workups

Changing gears.

Stroke Subtypes and Management

- Tempo
  - Completed
  - *"Stroke in evolution"*
- Stroke Type
  - Large artery atherosclerotic
  - Cardioembolic +/- AF
  - Lacunar
  - Cryptogenic
  - Hemorrhagic

Stroke Workup

- Neuroimaging
  - NCHCT
    - Hemorrhagic: HTN, amyloid?
  - Brain MRI
    - Embolic, watershed, lacunar ?
  - Head and neck MRA to aortic arch
    - Proximal vertebral/carotid stenosis, carotid bulb stenosis, irregularity or plaque?
  - Carotid U/S
    - Flow hemodynamics, plaque character ?

Stroke Workup

- Neuroimaging (cont)
  - Cerebral angiography: vasculitis, intracranial atherosclerosis?
- Cardiovascular/medical evaluation
  - TTE or TEE: cardioembolism, PFO, ASD/VSD, cardiomyopathy?
  - Troponin I, lipid panel, HBA1c
- Stroke in the young workup
  - Tox screen
  - ESR, ANA, RPR

Stroke Workup

- Stroke in the young workup (cont)
  - Factor V Leiden mutation
  - Prothrombin 20-210A mutation
  - Protein C & S deficiencies
  - β_2-glycoprotein Abs
  - Lupus anticoagulant
  - Anticardiolipin Abs
  - Antithrombin III activity
  - Homocysteinemia

Neurological Complications

- Progression of thrombosis
- Recurrent embolism
- Increased intracranial pressure
  - Coma
  - Herniation
  - Hemorrhagic transformation
  - Hydrocephalus
  - False localization: *Kernohan's notch*
- Seizures

Medical Complications

- aMI, CHF, arrhythmia
- Aspiration pneumonia, UTI, sepsis
- DVT, PE
- GIB
- Hypoventilation, inability to protect airway
- Hypertension
- Electrolyte, glucose derangements
- Decubiti
- Depression

Anticoagulation or Antiplatelet Rx?

Evidence based stroke neurology

Antiplatelets and Acute Stroke

- Antiplatelets
  - ASA
  - Ticlid
  - Plavix
  - Aggrenox (Dipyridamole/ASA)
- Only ASA evaluated (CAST)
  - “Within 48 hours of ischemic stroke, ASA saves 9 lives for every 1000 patients treated.”

Stroke 31(6):1240-9, 2000

Antiplatelet Agents ASA

- Irreversibly inhibits platelet cyclooxygenase, preventing TXA_2 formation and blocking platelet aggregation
- Lasts for platelet's life, or 7-10 days
- Antiplatelet Trialists' Collaboration *(BMJ 308:81, 1994)*
  - 325mg to 1300m/day
  - 22% relative risk reduction in high risk of stroke
- *81 mg/day*
- Contraindicated in symptomatic PUD or ASA intolerance

Antiplatelet Agents Thienopyridines

- Ticlopidine, clopidogrel
- Inhibit ADP-mediated platelet aggregation/adhesion by binding to platelet $P2Y_1$ receptor
- Animal data also suggests additional inhibition of $5\text{-}HT_2$ and endothelin-1 mediated vasoconstriction

Thromb Res 92:83, 1998

Antiplatelet Rx and Stroke Prevention

- TIA/stroke
  - Aggrenox 25/200 bid
    ASA 81mg qd
- TIA/stroke on ASA
  - Aggrenox 25/200 bid
- TIA/stroke in ASA intolerant or w/ significant CAD/PVD
  - Plavix 75mg qd

Anticoagulation: Heparin, Heparinoids and Coumadin

Why take

a knife to a gunfight?

Heparin/LMWH/Heparinoids "Bottom Line"

"*Consider* early anticoagulation in acute cardiogenic and large artery ischemic strokes and for progressing stroke when the suspected mechanism is *ongoing* thromboembolism."

Chest 119:330-21S, 2001

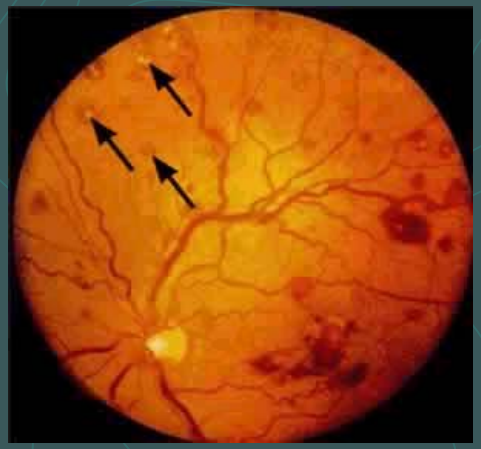
Heparin/LMWH/Heparinoids “Bottom Line”

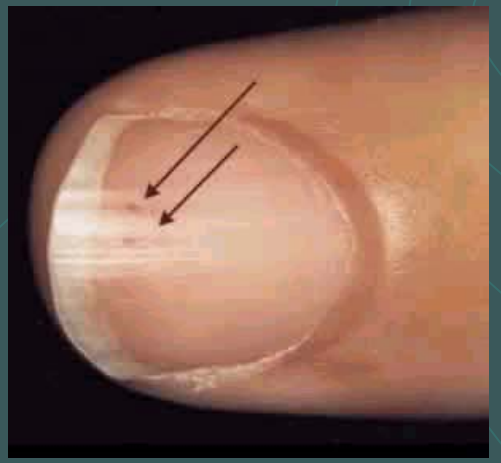
- Large artery atherosclerotic disease
- Non-AF cardiogenic stroke
  - EF < 29%
  - Established intracardiac thrombus
  - Valvular abnormalities, prosthestic valves
- AF*
- Concurrent aMI
- PE/DVT
- Sinus venous thrombosis
- Carotid or vertebrobasilar dissection

Caveat: Infective Endocarditis and Heparin

- NEVER USE HEPARIN IF ENDOCARDITIS AND SEPTIC EMBOLISM SUSPECTED
  - Stigmata of endocarditis
    - Roth spots, Osler's nodes, Janeway lesions, splinter hemorrhages, arterial insufficiency
  - Septicemia, bacteremia, FUO
  - Known portals: poor dentition, IV drug use
  - Valvular vegetations

Roth Spots, Osler Nodes, Janeway Lesions, Splinter Hemorrhages





Salmo trutta

Rip Collins' World Record Arkansas Brown Trout